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Drug Targeting into the Central Nervous System by Stereotactic Implantation of Biodegradable Microspheres

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CONTROLLED DRUG RELEASE in the central nervous system through an implantable polymeric vector has been developed in recent years. For this purpose, different polymeric devices composed primarily of synthetic biocompatible and biodegradable polymers have been investigated. The first polymeric devices developed were macroscopic implants (monolithic devices), which required open surgery for implantation. Microencapsulation methods, however, allow the production of microparticles or nanoparticles loaded with neuroactive drugs. Because of their size, these micro- or nanoparticles may be easily implanted by stereotaxy in discrete, precise, and functional areas of the brain without causing damage to the surrounding tissue. Presently, this method is most frequently applied in the fields of neuro-oncology and neurodegenerative diseases, but neurologically, the potential applications of drug targeting by stereotactic implantation of drug-loaded particles are legion. (Neurosurgery 34:1058–1064, 1994)

Key words: Biodegradable polymer, Drug delivery, Microspheres, Stereotaxy

Drug delivery to the central nervous system (CNS) remains a challenging area of investigation for both clinical and basic neuroscientists. For this purpose, a wide range of strategies has been developed, such as osmotic disruption of the blood-brain barrier, infusion pumps into cerebrospinal fluid, and implantation of tissue or cells (31, 34, 48, 65).

Advantageous new strategies have evolved from research in drug formulation: namely, controlled, sustained release and specificity of action from a vehicle driving the drug to the target itself. From this research, new drug forms were developed, allowing the controlled release of a drug for a definite and prolonged period (ranging from days to years), such as the polymeric monolithic implants (45).

The principle of incorporating a drug into an implantable polymeric vector for controlled release was first mentioned in the 1960s. At this time, Folkman and Long (25) demonstrated that a silicone rubber implanted into the myocardium of dogs could release low molecular weight drugs like digoxin. Since then, numerous polymer devices have been developed, often providing an imperfect release of high molecular weight drugs and/or causing problems in terms of biocompatibility (17, 29).

Poly(ethylene-co-vinyl acetate) was the first biocompatible polymer that provided successfully the controlled release of high molecular weight substances (44). A serious drawback to the use of these polymers as implants is their nonbiodegradability, which necessitates surgical removal after the drug is exhausted. To overcome this problem, the concept of biodegradable polymers for a sustained drug release began to be developed in the early 1970s. Biodegradable polymers may be defined as natural or synthetic polymers, which degrade in vivo, either enzymatically or nonenzymatically, to produce biocompatible nontoxic products. These can be further metabolized or excreted via normal physiological pathways. Many natural and synthetic biodegradable polymers have been investigated. Human serum albumin, collagen, and gelatin were studied previously, but their cost and the uncertainty of their purity restricted their use. Attention has therefore been focused on the synthetic biodegradable polymers, where the processing conditions, availability, and cost can be efficiently controlled, compared with the natural sources. Aliphatic poly-

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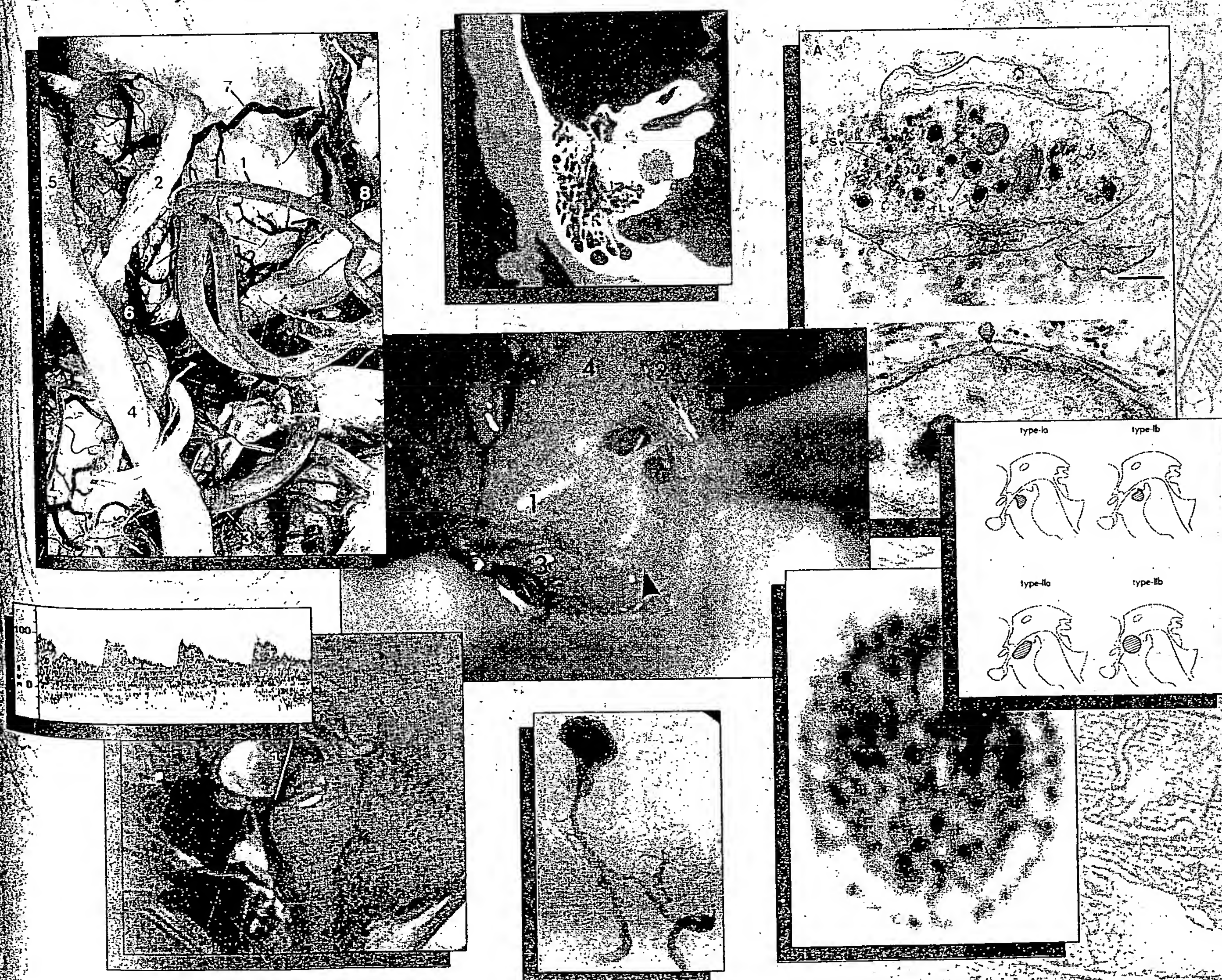

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esters, polyalkylcyanoacrylates, polyamino acids, polyorthoesters, and others are possible candidates as biodegradable drug carriers. Among them, the polyanhydrides and the poly(α-hydroxyacid)s have attracted the most attention (46, 60). The first application of a controlled release polymeric system in the brain was aimed at improving the labeling of perivascular meningeal projections from cat trigeminal ganglia (50). Since this study, different research groups, such as Langer's group (Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA) have developed biocompatible polymeric systems permitting the controlled and localized release of neuroactive substances directly into the brain (42).

The first polymeric devices developed were macroscopic implants also called monolithic devices. Drugs are incorporated into polymers by triturating dry powdered drug with similarly treated polymer and pressing weighed aliquots of the mixture in a press (trituration method) or by dissolving both the polymer and the drug in a solvent, evaporating the solvent, and pressing the resulting material (solution method). These macroscopic implants have the shape of a nail, disk, wafer, or pipe. Many implants have been prepared and studied for drug delivery into the brain of antimitotic drugs (9, 19, 30, 39, 58, 69, 81), corticosteroids (59, 70), angiogenesis inhibitors (66, 68), nerve growth factor (33, 57, 79), and dopamine (5, 23, 28, 78). Furthermore, macroscopic polymeric devices have been used for the treatment of glioblastomas in humans. Oda et al. (54) reported the first clinical trials with Silastic implants loaded with 5-fluorouracil and were followed by Kubo et al. (41) who used other drugs. No definite conclusions have been drawn from these studies because of the heterogenicity of treated tumors. Recently, Brem and coworkers (11, 14) extensively studied the interstitial chemotherapy of malignant gliomas with carmustine-loaded polymer devices. A phase I-II trial was performed with carmustine-loaded polyanhydride systems (13), and a multicentric phase III clinical trial is being conducted by the same group.

LINKAGE OF TWO CONCEPTS: MICROENCAPSULATION AND STEREOTACTIC NEUROSURGERY

For several years, we have explored the potential applications of micoencapsulation of therapeutic agents to provide controlled drug release in the CNS. Microparticles prepared by the classic microencapsulation methods usually range in size between 1 and 1000 μm (*Fig. 1*). Particles smaller than 1 μm are referred to as nanoparticles (38). Because of their size, these microparticles can be easily implanted by stereotaxy in discrete, precise, and functional areas of the brain without causing damage to the surrounding tissue (*Fig. 2*). This implantation avoids the inconvenient insertion of large implants by open surgery and can be repeated if required. For implantation, the microspheres can be injected in a suspension or as a powder

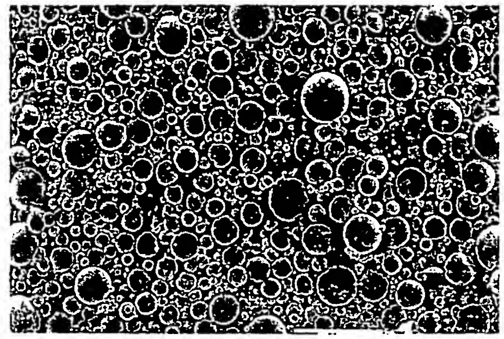

FIGURE 1. Scanning electron micrograph of PLAGA microspheres. The *bar* in the lower right corner represents 100 μm. The average sphere diameter is 27 μm.

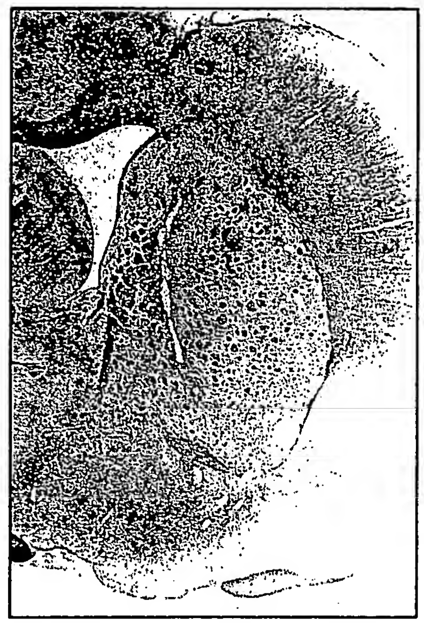

FIGURE 2. Photomicrograph of a brain section from a rat with PLAGA microspheres implanted into the striatum 10 days before (immunoperoxydase with anti-GFAP antibody, original magnification ×25).

with special needles. The size of these particles can be adapted to suit the target. Microspheres can be used for drug release in discrete regions of the brain. Nanospheres have been used for the retrograde labeling of neurons as they are taken up by fibers and transported back to the neuronal somata when they are injected into brain tissue (40). This property may be used for delivering drugs directly inside neural cells. Similarly, the uptake of nanospheres by astrocytes also has been observed in vitro (24).

MICROENCAPSULATION

The first research leading to the development of microencapsulation procedures was published by Bugenburg de Jong

and Kaas (10) in 1931 and dealt with the preparation of gelatin microcapsules by the coacervation process. In the late 1930s and 1940s, Green and co-workers from the National Cash Register Co., Dayton, Ohio, developed the gelatin coacervation process, which was covered by several patents to promote carbonless copy paper (71). Since then, many other coating materials, processes, and applications have been developed by the pharmaceutical industry. Other industries, such as the food, cosmetic, horticultural, paint, print, photographic, computer, fertilizers, adhesives, cleaning, and aerospace industries, have been concerned with microencapsulated products (18). At the same time, the plastics industry has been involved continuously in the production and evaluation of new polymers with a potential application in microencapsulation (55).

It is theoretically possible to microencapsulate all types of drugs and many processes for the preparation of micro- or nanoparticles have been reported in the literature (20):

- Physicochemical processes such as simple or complex coacervation for the preparation of microcapsules and also microspheres.
- Chemical processes such as interfacial polycondensation. This method requires two different bifunctional monomers; one is contained within the core material to be encapsulated (discontinuous phase), and the second is present in the continuous phase. The two monomers react at the interface of the dispersed droplets, causing polymerization and membrane formation.
- Mechanical processes, including pan coating, spray coating, and fluidized-bed coating.

Several different microparticle structures exist. There are two main types: the reservoir device and the matrix system. The reservoir device (microcapsules or nanocapsules) is a system in which the drug is confined to a cavity surrounded by a unique polymeric membrane. The matrix system (microspheres or nanospheres) is a system in which the drug is dispersed throughout the particle. The mechanisms of drug release are different, depending partly on the microparticle structure. In the reservoir device, the drug diffuses through a membrane. In the matrix system, the drug diffuses either through the polymeric mass or in the pores filled with water. If the polymer is biodegradable, a combination of diffusion and degradation phenomena regulates the release kinetics. Furthermore, it is possible to incorporate magnetite particles in the polymeric matrix for controlling the drug release by the application of an extracorporeal magnet (43).

COATING POLYMERS

A polymer is a compound made up from many molecular units assembled one to one, called monomers. When the polymer is composed of two different monomeric units, it is designated as a copolymer. Although many natural or synthetic polymers are available for the controlled release of drugs, only a few are suitable for the release of high molecular weight drugs. The first polymers used for making implantable devices were nonbiodegradable, such as polydimethylsiloxane (Silastic) or poly(ethylene-co-vinylacetate). Subsequently, other polymers have been experimented with, such as the acrylic or the vinyl compounds. Actually, the biodegradable polymers have been developed primarily for the medical field for evident reasons. Among them, the polyanhydrides and the aliphatic polyesters have been extensively studied. Their degradation is caused by the cleavage of the ester bond by hydrolysis.

The polyanhydrides are nonmutagenic, noncytotoxic, and nonteratogenic (46, 47), and their biocompatibility and biodegradability into the brain have been demonstrated (12, 67). Despite clinical trials in cancerology (13), this class of polymers still has not obtained any Food and Drug Administration approval for current clinical use.

The aliphatic polyesters include poly(α-hydroxyacid), poly(β-hydroxyacid), and poly(ϵ-caprolactone). Poly(ϵ-caprolactone) is a very slow biodegradable polymer, which has been studied for the design of subdermal implants (56). We have shown that poly(ϵ-caprolactone) microspheres implanted into the rat brain were not degraded until 9 months elapsed and were well tolerated (Menei et al., submitted for publication). Poly(β-hydroxyacid)s are constituted mainly by poly(β-hydroxybutiric acid) and poly(β-malic acid) and are widely studied (26). The poly(α-hydroxyacid)s are constituted of lactic and/or glycolic acid units. When the two types of monomeric units are associated along the same chain, copolymers are generated, poly(lactide-co-glycolide) (PLAGA) (*Fig.* 3). The degradation products of the copolymers are lactic and glycolic acids, which are natural metabolic products. The long history of the clinical use of these copolymers, particularly as surgical sutures, has demonstrated their excellent histocompatibility (27, 74). PLAGA microspheres are currently used in clinical practice as subdermal implants for the controlled release of luteinizing hormone-releasing hormone analogs.

The physicochemical and degradation properties of PLAGA depend on many parameters, such as the molar ratio of the two monomers in the polymer backbone and the molecular weight of the polymer. For instance, as the crystallinity of the material decreases or the glycolic unit content increases up to an optimal lactic acid/glycolic acid ratio of 50:50, the rate of degradation of the backbone increases. The biodegradation rate of the PLAGA copolymers may vary from less than 1 month to

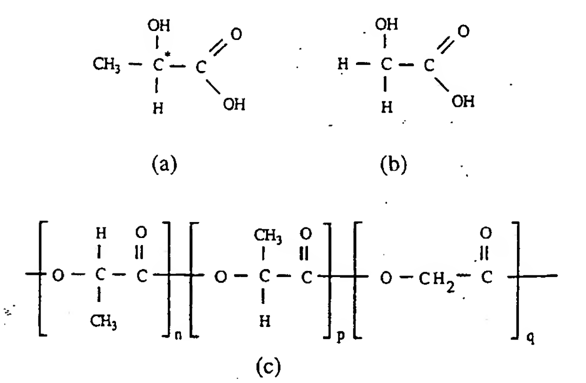

FIGURE 3. Structures of lactic acid (*a*), glycolic acid (*b*), and a copolymer (*c*). *n*, percentage of L-lactic units; *p*, percentage of D-lactic units; *q*, percentage of glycolic units.

a period of some years, depending on the polymer composition (63) and the size of the device (73). It can therefore be modified and adapted to suit clinical purposes. The PLAGA systems can be easily sterilized by γ-irradiation, despite the alteration of the polymer properties (63). We have established the brain compatibility of the PLAGA microspheres and studied their fate after stereotactic implantation in the rat brain (52). Current efforts in our laboratory are aimed at using this type of microsphere for drug delivery in the CNS.

APPLICATIONS OF SUSTAINED RELEASE OF DRUGS FROM MICROPARTICLES INTO THE CENTRAL NERVOUS SYSTEM

Neuro-oncology

The PLAGA microspheres can be loaded with antimitotic drugs, irrespective of their solubility profile. Hydrophilic drugs like 5-fluorouracil (8) as well as lipophilic ones like carmustine (Torres et al., submitted for publication) were successfully entrapped. 5-FU-loaded microspheres have been implanted in the brain of glioma-bearing rats and the mean of survival increased markedly (7). However, it is evident that future progress in neuro-oncology will come from the biotechnologies that generate very potent peptides and proteins. Microspheres will certainly allow the locally controlled release of cytokines for immunotherapy (53) and of new tumor-killing agents like tumor necrosis factor (80).

Neurodegenerative diseases

This field is the most exciting, and potential applications of the implantable microparticles can be expected. Neurotransmitters, neuromodulators, neurohormones, and trophic factors, which clearly play a substantial role in the activity and maintenance of the CNS are being discovered in increasing numbers. Delivery of such compounds to the brain will be a difficult problem to overcome with classic methods of drug administration. In addition, because of the complex chemoarchitecture of the CNS, drug delivery to a very restricted region of the brain is always required.

In some neurodegenerative diseases, there is a striking depletion of one or more neurotransmitters. Implanted microspheres carrying the appropriate pharmacological agent can restore neurotransmission. It is possible to attain functionally significant amounts of dopamine for a prolonged period of time by implantation of PLAGA microspheres loaded with this neurotransmitter into the rat striatum (49). Bethanechol (an acetylcholinesterase-resistant cholinomimetic), released by polyanhydride microspheres implanted into the hippocampus of rats having undergone a cholinergic denervation, reversed lesion-induced memory deficits (35).

More interesting is the sustained release of neurotrophic molecules. These molecules have a profound influence on developmental events such as naturally occurring cell death, differentiation and process outgrowth (32, 72), and could be used for treating degenerative neurological conditions and promoting neural regeneration. The best characterized trophic molecule, nerve growth factor, has a spectrum of effects on peripheral and central neurons. This peptide molecule cannot cross the blood-brain barrier and therefore needs to be administered directly into the brain. Biologically active nerve growth factor can be released over a 4.5-week period in vitro and in the brain from PLAGA microspheres (15).

The monoganglioside GM1 is a glycolipid that stimulates the reparative processes occurring after a brain lesion. It can be released in rat brain from serum albumin microspheres (51).

Microencapsulation methods also allow the loading of various cells, bacteria, viruses, and yeasts. The capsules allow both normal biological functioning (passage of nutrients, neurotransmitters, and other cell products) and protection of the contents from immunorejection. Although the brain is thought to be an immunoprivileged site, immunorejection of allo- and xenografts may occur (76). Macro- and microencapsulation of cells with a selectively permeable membrane allow immunoisolation from the host.

Microencapsulations of different types of cells (in particular, pituitary cells) through interfacial adsorption, interfacial precipitation, or microemulsion polymerization have been reported (22).

Not far from the microencapsulation technology, the techniques of macroencapsulation permit loading cells into hollow fibers that are subsequently closed at both ends with a polymeric glue. Aebischer et al. (4) used this procedure to encapsulate dopamine-releasing cells—embryonic mesencephalon, adrenal chromaffin cells, and an immortalized cell line, PC12, derived from a rat pheochromocytoma (1, 3, 36, 37). The same authors have demonstrated the feasibility and survival of macroencapsulated neural tissue transplantations (2, 77, 78).

Other potential applications

Currently, many other drugs have been incorporated into PLAGA microspheres, for example, hormones and hormone agonists (6, 61), neuroleptics (64), antimitotic drugs (8, 62), local anaesthetics (75), anti-inflammatory drugs (21), and steroids (16). The incorporation of other neuroactive drugs is being studied extensively, and other applications of microspheres are being investigated regarding chronic pain, spasticity, epilepsy, and neurological infections.

CONCLUSIONS

Targeting of drugs in the CNS by implantation of biodegradable microspheres is feasible and offers numerous theoretical advantages. The potential applications of these biodegradable microspheres for neurological diseases are legion. However, once the cerebral target is identified and the neuroactive drug is synthesized, work still remains before microparticle devices can be used therapeutically. For precise clinical purposes, the preparation, characterization, and evaluation of microparticle devices require some years in animal models.

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COMMENTS

This article provides a prospective on some novel biological strategies to introduce therapeutic agents into the brain. The matter is an important one because the blood-brain barrier is altered in disease to a variable and often to an insufficient degree. Sometimes, it is not altered at all. Nonlipid soluble drugs and larger molecules, such as monoclonal antibodies, are excluded largely by the brain's specialized endothelium. So are gene constructs, cells, many objective bioactive peptides, and a growing host of interesting substances with therapeutic possibilities. If stereotactically delivered, biodegradable microspheres have great potential to be used to advantage in targeting treatment to specific brain regions. Although this work remains chiefly experimental, it is exciting and worth knowing about now. Menei and his colleagues have provided an accessible and well-referenced glimpse into the future.

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The authors present an overview of the role of polymeric drug delivery in the brain. In particular, they describe their ongoing work utilizing polylactide microspheres for delivering drugs for localized release. They postulate that the microspheres would be particularly well suited for stereotactic implantation and retreatment when necessary.

The modeling of drug distribution in combination with precise stereotactic implantation potentially will allow for precise "drug" planning—similar to the approach taken for stereotactic radiation dosimetry planning.

The choice of polymer will depend on the application; for example, polycarboxyphenoxy propane anhydride with sebacic acid (which is clinically utilized) is ideal for releasing small lipid soluble compounds (1, 7). However, the fatty acid dimer polyanhydride has been shown to be superior for long-term release of water soluble agents such as carboplatin or 4-Hydroxyperoxycyclophosphamide (3). Polylactide polymers have different release characteristics and will therefore have a specific niche as well in the polymer-drug delivery armamentarium.

Although, ideally, the polymer should biodegrade with the release of the drug, there is no evidence that nonbiodegradable polymers necessarily have to be removed if there is no evidence of a short- or long-term deleterious effect. In fact, in general, nonbiodegradable polymers such as ethylene vinyl acetate copolymer poly(ethylene-co-vinyl acetate) are less reactive because they are simply inert implants. A potential drawback of the nonbiodegradable polymers is the desirability of not having any foreign material to serve as a possible nidus of infection. There is, however, a strong precedent for the neurosurgical use of nondegradable implants such as the silicone utilized in shunts.

We agree strongly that stereotactic implantation of a polymer with drugs greatly expands the ability to treat neurological disease selectively. On a simpler level, the polymer implants that have been extensively utilized in animal studies in the rat brain are easily inserted through a stereotactic trocar, for example, chemotherapeutic agents (2, 9), steroids (5, 10), antiangiogenesis agents (6, 8), and immunotoxins (4).

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